Executive Summary:

Indication: Tigecycline is a novel glycylcycline that exhibits expanded broad-spectrum antibacterial activity that includes antimicrobial-resistant pathogens, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, multidrug-resistant *Streptococcus pneumoniae,* extended-spectrum β-lactamase-producing Gram-negative bacteria, *Acinetobacter baumannii,* and bacteria with tetracycline resistance determinants. Tigecycline is not, however, active against some bacteria, such as *Proteus, Providencia* and *Pseudomonas* species. It is currently indicated for the treatment of complicated skin and skin structure (cSSS) as well as complicated intra-abdominal (cIAI) infections.

Dosing: The recommend dosing regimen for tigecycline is an initial dose of 100mg followed by 50mg IV every 12 hours infused over 30-60 minutes.

Efficacy: Results from randomized Phase III studies comparing the clinical and microbiological efficacy of tigecycline with combination antimicrobial therapy for the treatment of cSSSI and cIAI are encouraging. Based on limited data, tigecycline was found to be non-inferior to conventional antibiotics in the management of various complicated infections.

Safety: The most common reported adverse effect (>5%) in phase 3 trials were abdominal pain, fever, headache, infection, diarrhea, nausea/vomiting, thrombocytopenia, elevated hepatic enzymes, and injection site reactions. Nausea/vomiting was the most common adverse effect usually occurring during the first 1-2 days of treatment. It was the most common reason for discontinuation. Of note, in clinical trials, treatment-emergent adverse reactions that required tigecycline discontinuation occurred in 4.7% in the tigecycline groups in clinical trials versus 5.3% in vancomycin and 4.4% in imipenem-cilastin treatment groups. There was a non-significant incidence of death between treatment groups 2.3% (32/1383) in the tigecycline group versus 1.6% (22/1375) in the other antibiotic treatment groups. This difference was not statistically different.

Recommendations: Tigecycline may be advantageous with respect to the emergence of multidrug-resistance among some of these organisms and it may be an appropriate alternative in the management of difficult to treat infections where conventional antibiotics have failed or are contraindicated.

Formulary Status
Tigecycline is on the VANF restricted to Infectious Disease

National PBM Drug Monograph
Tigecycline (Tygacil™)
March 2006
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Introduction

Tigecycline is a novel 9-tert-butylglycylamido derivative of minocycline. It is a glycylcycline, a class of antibiotic discovered in 1993 by modification of the structure of the tetracycline molecule. Tigecycline acts via the same mechanism as tetracyclines but with a longer half-life and higher affinity to the 30S ribosome which enhances its spectrum of activity. Tigecycline is given intravenously and has activity against a variety of gram-positive and gram-negative bacterial pathogens, many of which are resistant to existing antibiotics. It is currently indicated for the treatment of complicated skin and skin structure as well as complicated intra-abdominal infections.

Clinical Pharmacology[1,2]

Tigecycline acts by binding to the 30S ribosomal subunit of susceptible organisms, interfering with the binding of tRNA to the mRNA-ribosome complex and subsequently preventing protein synthesis.

Tigecycline's spectrum of activity is similar to other tetracyclines, but also exhibits activity against tetracycline-resistant organisms that utilize efflux or ribosomal protection to infer resistance (the two most common mechanisms of tetracycline resistance). In addition, other forms of resistance due to beta-lactamases, target site modifications, macrolide efflux pumps or enzyme target changes (gyrase/topoisomerase) do not affect tigecycline's antimicrobial activity. No reports of cross-resistance among other antibiotics have been reported. Tigecycline is generally considered a bacteriostatic agent with notable activity against most gram-negative and gram-positive bacteria including Methicillin-resistant *Staphylococcus aureus* (MRSA), Vancomycin-resistant *Enterococcus spp.*, as well as numerous anaerobic organisms. Tigecycline also has decreased activity against *Morganella, Proteus*, and *Providencia spp.* However, *Pseudomonas spp.* are considered resistant to tigecycline.

Antimicrobial Activity[2]

Table 1. *In vitro* activity (MIC$_{90}$,ug/mL) of tigecycline and the tetracycline				
Bacteria	**Tigecycline**	**Tetracycline**	**Doxycycline**	**Minocycline**
Staphylococcus aureus (MS)	0.5	1	0.5	0.12
S. aureus (MR)	0.5	32	2	2
Staphylococcus epidermidis (MS)	0.5	2	NA	0.5
S. epidermidis (MS)	0.5	>8	NA	4
Staphylococcus saprophyticus	0.5	0.5	NA	NA
Streptococcus pyogenes	0.06	4	0.5	0.25
Streptococcus agalactiae	0.12	64	16	32
Streptococcus pneumoniae	0.125	32	8	8
S. pneumoniae (PI)	0.06	64	8	16
S. pneumoniae (PR)	0.125	64	8	16
Escherichia coli	0.5	>8	NA	8
Haemophilus influenza	1	0.5	3.1	0.25
H. influenza (BLP)	2	1	NA	1
Klebsiella pneumoniae	1	4	NA	4
Klebsiella spp.	0.5	128	NA	NA
Moraxella catarrhalis	0.12	0.25	NA	0.06
Morganella morganii	8	16	NA	4
Neisseria gonorrhoeae (PS,PR)	1	?32	2	32
Neisseria meningitides	0.12	0.25	NA	0.12
Proteus mirabilis	8	32	NA	16
Proteus vulgaris	8	32	NA	>8
Providencia rettgeri	8	>8	NA	>8
Providencia stuartii	8	>8	NA	>8
Pseudomonas aeruginosa	16	16	NA	32
Burkholderia cepacia	32	2	NA	2
Salmonella spp.	0.5	2	NA	16
Serratia marcescens	2	>8	NA	8
Shigella spp.	0.5	32	NA	4
Stenotrophomonas maltophilia	4	4	NA	1
Yersinia enterocolitica	0.5	1	NA	1
Bacteroides fragilis	2	32	8	8
B. fragilis group	4	32	4	4
Clostridium difficile	0.125	0.125	0.125	0.032
Clostridium perfringins	0.25	8	0.125	0.125
Fusobacterium spp.	0.06	0.25	0.125	0.06
Peptostreptococcus spp.	0.125	16	4	8
Chlamydia pneumoniae	0.125	NA	0.25	NA
Legionella pneumophilia	NA	1-8	4	4
Mycoplasma pneumoniae	0.25	1	1.6	1
Ureaplasma urealyticum	NA	NA	NA	NA

MR = methicillin resistant; MS = methicillin sensitive; **NA** = information not available; **PI** = penicillin intermediate; **PR** = penicillin resistant; **PS** = penicillin susceptible; **BLP** = beta lactamase-positive; **NA** = information not available; **PR** = penicillin resistant; **PS** = penicillin susceptible

Tygacil Package Insert. Philadelphia, PA: Wyeth Pharmaceuticals; 2005 June.

Pharmacokinetics[1,3]

Tigecycline is extensively distributed throughout plasma and body tissue following IV administration with a volume of distribution of 7-9L/kg. Following administration of a standard regimen in healthy volunteers, AUC_{0-12} in alveolar tissue was 78-fold higher than serum AUC_{0-12}, 32% higher in epithelial fluid, and 26% lower in blister fluid. Tigecycline concentrations in gallbladder, lung, colon, and bone were higher compared to serum concentrations at 4 hours following a single 100mg tigecycline IV dose.

Tigecycline is not extensively metabolized in the liver – only trace amounts of metabolites were noted in *in vitro* studies using human liver enzymes. Tigecycline is mainly eliminated unchanged via biliary/fecal excretion (59%), followed by renal elimination (33%, of which 22% is eliminated unchanged in urine).

FDA Approved Indications

- Complicated infection of skin AND/OR subcutaneous tissue
- Complicated intra-abdominal infections
- Off-label = other infections caused by multi-drug resistant organisms – including pneumonia and osteomyelitis.

Current VA National Formulary Status

Tigecycline is not currently on VA National Formulary

Dosage and Administration[3]

Tigecycline is given intravenously. The recommend dosing regimen for tigecycline is an initial dose of 100mg followed by 50mg IV every 12 hours infused over 30-60 minutes.

Duration of therapy:
- Complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days.
- The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Special Populations:
- **Mild to moderate hepatic impairment:** No adjustment is warranted
- **Severe hepatic impairment (Child Pugh C):** Initial dose should be 100mg followed by 25mg IV every 12 hours.
- **Renal impairment:** No adjustment is necessary
- **Age, gender, race:** No dosage adjustments are needed for age, gender or race

- **Pregnancy and Nursing:** Tigecycline is classified as Category D. Tigecycline should only be used in pregnant women if risks outweigh benefits
- **Pediatrics:** Tigecycline has not been adequately studied in patients <18 years of age. Tigecycline is not recommended for use in this patient population
- **Geriatrics:** No differences were observed among aged populations, but increased sensitivity to adverse effects is not unexpected

Preparation/Administration. Each vial of tigecycline should be reconstituted with 5.3 ml of 0.9% sodium chloride or 5% dextrose to achieve a concentration of 10 mg/mL. Once dissolved, 5 mL of the reconstituted solution should be withdrawn from vial and added to a 100 mL IV bag for infusion. The maximum concentration in the IV bag should be 1mg/mL and administered over approximately 30 to 60 minutes every 12 hours. Reconstituted solution must be immediately transferred and further diluted for IV infusion. It may be stored in the IV bag at room temperature for up to 6 hours, or refrigerated at 2 to 8°C (36 to 46°F) for up to 24 hours. The reconstituted solution should be yellow to orange in color; if not, the solution should be discarded.

Tigecycline demonstrates Y-site or in-line compatibility with 0.9% sodium chloride and 5% dextrose. If the same IV line is used for sequential infusion of several drugs, the line should be flushed before and after infusion of tigecycline with either 0.9% sodium chloride or 5% dextrose. If administered through Y-site line, tigecycline is compatible with the following drugs or diluents: dobutamine, dopamine HCl, lactated Ringer's, lidocaine HCl, potassium chloride, ranitidine HCl, and theophylline. The following drugs should not be administered simultaneously through the same Y-site line: amphotericin B, chlorpromazine, methylprednisolone, and voriconazole.

Information For The Patient

This medicine should be given by a person trained to give IV medicine, such as a nurse.

Adverse Effects (Safety Data)[1,3]

- Deaths and Other Serious Adverse Events
  - There was a non-significant incidence of death between treatment groups 2.3% (32/1383) in the tigecycline group versus 1.6% (22/1375) in the other antibiotic treatment groups. This difference was not statistically different. Infection-related adverse effects was higher in the tigecycline group (6.7%) versus other antibiotics (4.6%). There was a statistically significant increase in the incidence of sepsis in the tigecycline treated patients, but the majority of patients had complicated comorbid conditions and a relationship could not adequately be established.
- Common Adverse Events (>5%)
  - The most common adverse effects (>5%) in phase 3 trials were abdominal pain, fever, headache, infection, diarrhea, nausea/vomiting, thrombocytopenia, elevated hepatic enzymes, and injection site reactions.

Nausea/vomiting was the most common adverse effect usually occurring during the first 1-2 days of treatment. It was the most common reason for discontinuation. Of note, in clinical trials, treatment-emergent adverse reactions that required tigecycline discontinuation occurred in 4.7% in the tigecycline groups in clinical trials versus 5.3% in vancomycin and 4.4% in imipenem-cilastin treatment groups.

- Other Adverse Events
  - o Other adverse effects that occurred infrequently (0.2%-2%) during phase 3 clinical trials include: injection site inflammation, injection site pain, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis, thrombophlebitis, bradycardia, tachycardia, vasodilatation, anorexia, dry mouth, jaundice, abnormal stools, increased creatinine, hypocalcemia, hypoglycemia, hyponatremia, somnolence, taste perversion, prolonged activated partial thromboplastin time, prolonged prothrombin time, eosinophilia, increased international normalized ratio, thrombocytopenia, vaginal moniliasis, vaginitis, leukorrhea.

Table 2: Incidence (%) of Adverse Events in Patients Treated With Tigecycline in Phase 3 Clinical Studies				
	cIAIs		cSSSIs	
Body system adverse event	Tigecycline (N = 817)	Imipenem-cilastatin (N = 825)	Tigecycline (N = 566)	Vancomycin-aztreonam (N = 550)
Any	73.8	71.6	67.7	61.1
Body as a whole	35.4	31.5	27.7	24.2
Abdominal pain	8	6.7	3.2	2
Fever	9.1	12	2.3	4.9
Headache	3.4	5.8	8.7	6.7
Infection	10.2	5.5		
Pain			4.8	3.1
Cardiovascular system	14.8	18.3	8.8	14.7
Hypertension	6	6.2	2.5	4.5
Phlebitis	2	4	1.6	3.1
Digestive system	44.4	39.4	45.6	20.5
Anorexia			3.4	0.4
Constipation	2.6	3.5	2.5	4
Diarrhea	13.8	13.2	8.5	5.1
Dyspepsia			3.7	0.9
Nausea	24.4	19	34.5	8.2
Vomiting	19.2	14.3	19.6	3.6
Hemic and lymphatic system	15.1	15	11.8	10.2
Anemia	4.8	5.2	1.8	3.6
Leukocytosis	4.4	2.4		
Thrombocythemia	6	6.4		
Activated partial throboplastin time prolonged			3.5	1.5
Prothrombin time prolonged			3.2	0.9
Metabolic and nutritional	26.3	26.3	16.8	17.6
Alkaline phosphatase increased	4	2.5		

Healing abnormal	4.5	2.9		
Hypokalemia	2.3	3.2		
Hypoproteinemia	5.9	3.6		
Lactate dehydrogenase increased	4.7	4.5		
Peripheral edema	3.7	4.4		
AST increased	2.9	3.4	1.8	5.1
ALT increased	3.3	2.8	1.4	6.2
Respiratory system	16.9	15.8	5.3	6.9
Cough increased	4	4.8		
Dyspnea	3.7	2.8		
Pulmonary physical finding	3.1	3.4		
Adverse event assoc with miscellaneous factors	11.6	11.6	3.4	3.8
Local reaction to procedure	11.5	11.6	3.4	2.9
Skin and appendages			10.6	19.3
Pruritis			4.2	7.3
Rash			1.9	5.8
Urogenital system			3.4	3.8

cIAI = *complicated intra-abdominal infections*, cSSSI = complicated skin and skin structure infections

Precautions and Contraindications

- Precautions
    - Hypersensitivity to tetracycline class antibiotics
    - Pregnancy
    - Usage in newborns, infants, and children less than 8 years old (risk for tooth discoloration)

- Contraindications
    - Hypersensitivity to tigecycline

Look-alike/Sound-alike (LA/SA) Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage forms, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

- LA/SA for trade name Tygacil:
    - Severity Category: major
        - Fluorouracil, Adrucil, Adriamycin RDF, Cisplatin, Doxil, Idamycin, Mithracin, Mitomycin, Mutamycin

    - Severity Category: minor-moderate
        - Tagamet, Pipracil, Totacillin-N, Diuril sodium, Ticarcillin disodium, Triavil, Tridil, Kytril, Mycamine, Tigan, Tusal

- LA/SA for generic name tigecycline:
    - Severity Category: major
        - Mitomycin

    - Severity Category: minor-moderate
        - Tetracycline HCl, Timentin, Ticarcillin Disodium, Ticar, Terramycin

Drug Interactions[1, 3]

Tigecycline is not metabolized by the following CYP450 liver enzymes: CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Tigecycline is not expected to be effected by drugs that induce or inhibit these enzymes or in patients with impaired hepatic function.

Tigecycline has been found to inhibit the clearance of the R and S-warfarin enantomer by 40 and 23%, increase C_{max} by 38% and 43%, and increase AUC by 68% and 29%, respectively. Although tigecycline did not affect INR significantly, it is recommended that warfarin coagulation be monitored closely. Tigecycline's pharmacokinetics are not significantly affected by warfarin.

Tigecycline co-administration with digoxin resulted in increased digoxin C_{max}, but no change in AUC or clearance. No dosage adjustment is needed when used concomitantly.

Clinical Trials [4-6]

Complicated intra-abdominal infections (cIAI)
Tigecycline has been investigated in three studies, one open-label Phase II trial and two randomized, double-blinded Phase II clinical trials. The following is a summary from a pooled analysis of the two randomized, double-blind, active-controlled, multinational, multi-center studies with similar study methodologies.[4-5]

Citation	Babinchak T, Ellis-Grosse E, Dartois N et al. The efficacy and safety of tigecycline for the treatment of complicated intra-abdominal infections: Analysis of pooled clinical trial data. *CID* 2005;41:S354-367.
Study Goals	To evaluate the safety and efficacy of tigecycline versus imipenem-cilastatin in patients with complicated intra-abdominal infections.
Methods	Two phase 3, randomized, double-blind (third-party-unblinded) trials conducted from November 2002 to May 2004. Patients were randomized to receive either tigecycline (initial dose of 100mg, followed by 50mg IV q12h) or imipenem-cilastatin (500/500mg IV q6h) for 5-14 days.
Criteria	Subjects were eligible for the study if they were >18 year old and required surgery to treat a complicated intra-abdominal infection. Complicated IAI's could include: intra-abdominal abscess, appendicitis complicated by perforation/abscess, perforated diverticulitis with abscess or fecal contamination, etc. Exclusion criteria included suspicion of spontaneous

	bacterial peritonitis, cholecystitis, gangrenous choleystitis without rupture, simple appendicitis, acute supurative cholangitis, pancreatic abscess or infected necrotizing pancreatitis; APACHE II score >30; active or treated leukemia; AIDS; uncontrolled CNS disease; pregnancy or breast-feeding among women; liver dysfunction or significant hepatic disease (AST, ALT >10 time ULN; Normal or total bilirubin >3 times ULN), acute, chronic hepatic failure; significant renal disease (CrCl <41mL/min/1.73m^3 after hydration); neutropenia (defined as ANC <1000 cells/mm^3 – counts as low as 500 cells/mm^3 permitted if felt secondary to infections process); surgical procedures requiring fascia or deep muscular layers to be left open or expectation of planned abdominal re-exploration; administration of intra-operative antibacterial irrigants or peritoneal antibacterial agents. Patients that met study inclusion and exclusion criteria were randomized into the tigecycline group (100mg IV initial dose followed by 50mg every 12 hours) or the imipenem/cilastin group (500mg IV every 6 hours) for 5 to 14 days. Baseline demographics and characteristics were similar between the treatment groups. The study subjects were considered to be moderately ill with APACHE scores <15. Approximately 50% in each group had complicated appendicitis. At baseline, 10% of subjects had a history of antibiotic failure, 22.5% of subjects had evidence of fecal contamination, 76.9% of subjects had bacterial documentation, 31.9% of subjects had large abscesses >100mL, and 10.7% of subjects had multiple abscesses.
Results	The primary endpoint of the study was clinical cure at the test-of-cure visit at 12-42 days after the first dose. Secondary endpoints included bacteriologic response rates and clinical response rates of monomicrobial versus polymicrobial and stratified isolates. A total of 1,658 subjects were enrolled, of which 1,025 (512 tigecycline, 513 imipenem-cilastin) were clinically evaluable and had pretherapy isolates identified for the microbiologic analysis. The results of the pooled analysis revealed a clinical cure rate of 86.1% in the tigecycline group versus 86.2% in the imipenem-cilastin group (95% CI – 4.5% to 4.4%, p<0.0001 for non-inferiority). Similarly, in the microbiologically modified intent-to-treat population, clinical cure rates were 80.2% and 81% (95% CI, -5.8% to 3.2% p<0.0001 for noninferiority), respectively. Overall, higher cure rates were noted in patients with monomicrobial infections versus polymicrobial infections in both groups. Bacterial eradication in the tigecycline group was 86.1% versus 86.2% in the imipenem-cilastin group (95% CI, -4.5% to 4.4% p<0.0001 for noninferiority). The authors noted tigecycline was statistically efficacious and noninferior to imipenem-cilastin. A total of 1,625 patients were evaluated for adverse drug effects for a median of 7-8 days. It was noted that adverse drug effects that occurred in at least 3% of subjects were similar between study groups. The most common adverse

	drug effects were nausea, vomiting and diarrhea. The incidence of nausea (24.4% tigecycline, 19% imipenem-cilastin, p=0.010) and vomiting (19.2% tigecycline, 14.3% imipenem-cilastin, p=0.008) were significantly higher in the tigecycline group. During the study period, one patient died from septic shock in the tigecycline group, this was attributed to antibiotic treatment failure.
Conclusions	Tigecycline is efficacious and well-tolerated in the management of complicated intrabdominal infections.

Complicated skin and skin structure Infections (cSSSI)

Tigecycline has also been evaluated in two phase III clinical trials with similar methodologies in the treatment of complicated skin and skin structure infections.[6] The following is a summary of a pooled analysis of the two clinical trials.[7]

Citation	Ellis-Grosse EJ, Babinchak T, Dartois N et al. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: Results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *CID* 2005;41:S341-353.
Study Goals	To evaluate the clinical efficacy and safety of tigecycline alone versus combination vancomycin-aztreonam in the management of complicated skin and skin structure infections.
Methods	Two phase 3, randomized, double-blind studies in hospitalized adults with complicated skin and skin-structure infections (cSSSI) from August 2001 to February 2004. Patients were randomly assigned (1:1) to receive tigecycline with placebo or the combination of vancomycin-aztreonam IV for up to 14 days. Patients in tigecycline group received tigecycline 100mg, followed by 50mg IV BID infused for 60 min. After each tigecycline infusion, patients received 100 mL of normal saline placebo infused for 60 min to maintain study blinding. Patients in vancomycin-aztreonam group received vancomycin (1 g IV BID) plus aztreonam (2 g IV BID).
Criteria	Exclusion criteria included patients presenting with necrotizing fasciitis, gangrene, osteomyelitis, plasmapharesis, hemoperfusion, neutropenia, impaired arterial blood supply and hepatic disease (AST, ALT >10 time ULN; Normal or total bilirubin >3 times ULN), or isolation of pseudomonas from baseline culture. Patients who met study inclusion criteria were randomized to receive up to 14 days of tigecycline (100mg IV followed by 50mg every 12 hours) or combination vancomycin (1g IV every 12 hours) with aztreonam (2g IV every 12 hours). Vancomycin was adjusted based on renal function. To maintain blinding, a 100mL infusion of normal saline was administered following the tigecycline infusion. The primary endpoint was clinical cure. The secondary endpoint was to compare microbiological efficacy between treatment groups.

Results	Baseline patient demographics were similar between treatment groups in both trials. Patient characteristics were also similar between treatment groups in terms of infection type, etiology of disease, and co-morbid conditions at baseline. A total of 1,129 patients were randomized to tigecycline or combination vancomycin-aztreonam groups. In the clinical modified intent-to-treat group (group with evidence of complicated skin and skin structure infection but no pretherapy culture isolates), clinical cure was obtained in 79.7% in the tigecycline group versus 81.9% in the vancomycin-aztreonam group (95% CI for difference, -7.1% to 2.8%, $p<0.001$) for non-inferiority. A total of 540 subjects (279 tigecycline, 261 vancomycin-aztreonam) were evaluable for organism isolated baseline pretherapy culture data. Clinical cure was obtained in 86.5% in the tigecycline group and 88.6% in the vancomycin-aztreonam group (95% CI for difference, -6.8% to 2.7%, $p<0.001$). Overall, there was no statistical difference between these primary study populations. There was no statistical difference between treatment groups in microbiological response and eradication. A total of 1,116 subjects in the modified intent-to-treat population (subjects that received at least one dose of antibiotic) were included in the evaluation of adverse drug effects. Overall, 67.7% of the tigecycline treatment group experienced adverse effects, compared to 61.1% in the vancomycin-aztreonam treatment group. The majority of these adverse effects were not related to the study drug and were mild-moderate in intensity. Digestive disorders including anorexia, diarrhea, dyspepsia, nausea, and vomiting, were significantly more prevalent in the tigecycline group versus the vancomycin-aztreonam group (46% versus 21%, respectively, $p<0.001$). Cardiovascular, skin/appendage adverse drug effects and elevated liver enzymes were more prevalent in the vancomycin-aztreonam treatment group. No hematologic or serum chemistry abnormalities were noted in the tigecycline treatment group. A total of seven patients died during the study period. Six of whom were from the tigecycline treatment group. The clinicians could not relate deaths to antibiotic treatment failure.
Conclusions	Tigecycline is as safe and efficacious as combination vancomycin-aztreonam in the treatment of complicated skin and skin structure infections.

Acquisition Costs

Table 3. Cost-Analysis of various intravenous antibiotics for 7 to 14 days duration					
Drug	Strength	VAMC Acquisition Cost per Unit	Dose	VAMC Drug Cost per Patient	
				7 day	14 day
Tigecycline	50mg	$31.94	100mg x1 then 50mg q12h	$511.04	$958.26
Linezolid	600mg PO	$37.36	600mg q12h	$523.04	$1,046.08
	600mg IV	$48.57		$679.98	$1,359.96
Quinupristin/ dalfopristin	350mg/150mg	$62.21	q8-12h	$870.94 $1,306.41	$1,741.88 $2,612.82
Imipenem/ cilastatin	500mg/500mg	$15.24	500mg q6h	$426.72	$853.44
	250mg/250mg	$8.22	250mg q6h	$230.16	$460.32
Piperacillin/ Tazobactam	4g/0.5g	$13.15	q6-8h	$276.15 $368.20	$552.30 $736.40
	3g/0.375g	$10.07	q6-8h	$211.47 $281.96	$422.94 $563.92
	2g/0.25g	$6.60	q6-8h	$138.60 $184.80	$277.20 $369.60
Vancomycin	1000mg	$3.72	q12h	$52.08	$104.16

Cost Analysis
Tigecycline injection is used on an inpatient basis. Thus, no VISN cost analysis data is available.

Conclusions
Tigecycline is a novel glycylcycline that exhibits expanded broad-spectrum antibacterial activity that includes antimicrobial-resistant pathogens, e.g. methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, multidrug-resistant *Streptococcus pneumoniae,* extended-spectrum β-lactamase-producing Gram-negative bacteria, *Acinetobacter baumannii,* and bacteria with tetracycline resistance determinants. Tigecycline is not, however, active against some bacteria, such as *Proteus, Providencia* and *Pseudomonas* species. Results from randomized Phase III studies comparing the clinical and microbiological efficacy of tigecycline with combination antimicrobial therapy for the treatment of cSSSI and cIAI are encouraging. Based on limited data, tigecycline was found to be non-inferior to conventional antibiotics in the management of various complicated infections. Thus, tigecycline may be advantageous with respect to the emergence of multidrug-resistance among some of these organisms and it may be an appropriate alternative in the management of difficult to treat infections where conventional antibiotics have failed or are contraindicated.

Formulary Status
Tigecycline is on the VANF restricted to Infectious Disease

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Prepared By: Truc N. Le
Pharm.D. Resident

Reviewed By: Jennifer Jordan, Pharm.D

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